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Investigating the Effect of Hemoperfusion Therapy on Laboratory and Clinical Factors in COVID-19 Patients: A Cross-Sectional Study

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ABSTRACT

Background: With the epidemic of the emerging COVID-19 disease in the world in 2019 and the lack of a definitive and effective treatment for it, medical science practically faced a new challenge, this study aimed to investigation the effect of hemoperfusion therapy on laboratory and clinical factors in COVID-19 patients. .
Materials & Methods: In this cross-sectional study, 49 patients with severe COVID-19, who had indications for hemoperfusion were examined in 2020-2021. The patients underwent four hemoperfusion sessions after inserting a vascular catheter and preparing a special filter. Changes in laboratory and clinical factors before and after each hemoperfusion session were carefully recorded, and the data were analyzed using SPSS software.
Findings: The results of the study showed that the average age of the patients was 55.5 ± 13.9 years. Changes in the patients' blood oxygen saturation levels after each hemoperfusion session showed a statistically significant improvement trend, the average values before and after the first session were 86.7±7.2% and 88.5±5.7%, respectively, indicating a significant increase (p= .009). Also, the inflammatory factor CRP (C-reactive protein) and blood platelet levels were significantly reduced after each hemoperfusion session.
Conclusion: This study showed that hemoperfusion could improve patients' blood oxygen saturation values without causing any special complications and could also have a clear effect on clearing inflammatory factors and CRP from the blood.

Keywords: Hemoperfusion, COVID-19, Clinical factors

CITATION LINKS

[1] Hu B, et al. Characteristics of... [2] Maxmen A. Divisive COVID 'lab leak' debate... [3] Soy M, et al. Cytokine storm in COVID-19... [4] Tabibzadeh A, et al. Investigation of... [5] Laboratory testing for 2019 novel coronavirus... [6] Bhaskar S, et al. Cytokine storm... [7] Smail SW, et al. Deciphering gender disparities in... [8] Rothan HA, Byrareddy SN. The epidemiology... [9] Bi Q, Wu Y, et al. Epidemiology and... [10] Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of... [11] Mitev V. Comparison of treatment of... [12] Wang CC, et al. Airborne... [13] Ronco C, Piccinni P, Kellum J. Rationale of... [14] Ankawi G, et al. What have we... [15] Soleimani A, Taba SM, Taheri SH, Loghman A, Shayestehpour M. The effect of... [16] Ronco C, Navalesi P, Vincent JL. Coronavirus epidemic... [17] Park S, et al. Hemoperfusion... [18] Organization WH. Infection prevention and... [19] Mathew G, et al. Strocss 2021... [20] Alavi Darazam I, et al. Efficacy of... [21] Mikaeili H, et al. The early... [22] Gómez-Rial J, Rivero-Calle I, Salas A, Martinon-Torres F. Role of... [23] Zhao Z, Wei Y, Tao C. An enlightening... [24] Tsang HF, et al. An update on... [25] Abbasi S, et al. Hemoperfusion... [26] Asgharpour M, et al. Effectiveness of... [27] Najafi A, et al. Evaluation of... [28] Surasit K, Srisawat N. The efficacy of... [29] Peng J-Y, Li L, Zhao X, Ding F, Hou X, Peng Z. Hemoperfusion... [30] Wu Z, McGoogan JM. Characteristics of and... [31] Siasat A, et al. POS-875 the... [32] Montazersaheb S, et al. COVID-19... [33] Zhang C, Wu Z, Li J-W, Zhao H, Wang G-Q. Cytokine release... [34]Taheri SV, Roshan K, Kaviani P, Pezeshgi A. On the occasion of...

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Introduction

Coronaviruses are a diverse group of viruses that infect various animals and could cause mild to severe respiratory infections in humans. The first case of coronavirus disease-2019 (COVID-19) was discovered in December 2019 in Wuhan, China, and quickly spread throughout China and from there to the rest of the world due to its highly transmissible nature, forming a very large pandemic.

The World Health Organization announced the beginning of a public health emergency on January 20, 2020, which finally ended after 3 years on May 5, 2023 [1-4]. About 770 million cases were infected with the virus, with 6.95 million deaths resulting from of this pandemic, which is significant in its own right and ranks this pandemic as the fifth deadliest pandemic in history [5-7].

Studies have shown that the actual number of infected cases is much higher than the positive cases identified and recorded, reaching more than one billion people. Also, regarding the actual number of deaths, it is estimated that between 16.5 and 26.5 million people have died due to this disease [8-10].

Since the beginning of the COVID-19 pandemic, different treatment methods have been used and investigated. There are some FDA (Food and Drug Administration)-approved drugs for COVID-19, such as paxlovid, remdesivir, and molnupiravir, whose clinical effectiveness has been proven [11].

These treatment processes include both methods of dealing with the virus and methods that affect the host's immune system [12].

In order to clean inflammatory mediators from the blood, therapeutic methods are available under the name of extracorporeal blood purification (EBP) therapies, which include hemodialysis, hemofiltration, hemoperfusion, plasma replacement, etc. The goal of all these methods is to clean and remove unwanted molecules from the bloodstream using different absorbent levels and settings depending on the molecules in question [13].

One of these methods is hemoperfusion, which could be used to remove pro-inflammatory cytokines that occur in inflammatory processes caused by sepsis and the cytokine storm that may subsequently occur , resulting in shock in the hemodynamic system and damage and dysfunction.

Using this method, multiple organ failure could be reduced [14, 15]. This treatment method has been used as a life-saving and final treatment for patients with most drug poisonings (such as poisoning with salicylates, ethylene glycol, etc.) and septic shock as well as in inflammatory procedures in the field of intra-abdominal infections and surgeries related to cardiovascular diseases [16].

As mentioned, hemoperfusion is an important treatment method for patients with systemic inflammatory response to remove mediators and inflammatory cytokines from the blood.

However, complications such as decreased blood platelet levels and subsequent increased risk of bleeding, decreased blood pressure in patients, decreased blood calcium levels, and temporary decreased white blood cell counts have led to restrictions on its use in the last two decades [17].

Objectives: Considering that studies conducted with clinical purposes on this treatment method are very limited, this study aimed to closely investigate the effect of hemoperfusion therapy on laboratory and clinical factors in COVID-19 patients.

Materials and Methods

Study design and study population: This cross-sectional study was conducted on all COVID-19 patients who, according to the World Health Organization (WHO) guidelines [18], suffered from a severe form of this disease, had indications for receiving hemoperfusion, and were treated and hospitalized

in Sayad Shirazi hospital in Gorgan during 2020-2021.

Inclusion criteria: All patients who suffered from severe acute COVID-19 and were admitted to the ICU (intensive care unit) (respiratory rate>24, heart rate>100 beats/min, SpO_2<90% at ambient air) were included in the study if they had one of the following conditions: laboratory evidence of significant increase in inflammatory cytokines (such as IL-6> 1000 pg/mL or 10 ng/mL, CRP> 3 +, lactate> 4 mmol/L, and ferritin> 1500 ng/mL); refractory vasoplegic shock (0.3 min/kg/gr –micro < NE); need for a second vasopressor; confirmed involvement of more than two vital organs (lungs, kidneys, liver, and heart); AKI (acute kidney injury) requiring RRT (renal replacement therapy); and acute respiratory distress syndrome (ARDS).

Exclusion criteria: Patients with any of the following conditions were excluded from the study: thrombocytopenia (Plt > 20,000), any known allergies to cartridge components, acute crisis due to sickle cell anemia, pregnancy, history of heparin-induced thrombocytopenia (HIT), and severe obesity (BMI > 40)

Data collection: In this study, data were collected using a checklist designed based on information available in the patients' files, including age and sex, history of diabetes and hypertension, duration of hospitalization, and outcome (death or recovery). First, all the studied patients who suffered from the severe form of COVID-19 and had indications for initiating hemoperfusion based on defined criteria were given the necessary explanations about the treatment method, its side effects, and consequences, and informed consent was obtained from the patient or his/her guardian or legal guardian. Then a temporary catheter was placed for vascular access.

After placing the vascular catheter and providing an absorbent filter, the patients were subjected to hemoperfusion. At first, two 4-hour sessions were conducted with an interval of 12 hours, and then a 4-6-hour session was performed daily for two days.

Basic information about the patient's clinical symptoms, oxygen saturation level, excretion factors (urea, creatinine, and albumin), and laboratory signs including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white blood cells (WBC), hemoglobin (Hb), platelets, lymphocytes, serum electrolytes (calcium, potassium, sodium, and phosphorus), and coagulation factors like prothrombin time (PT) and partial thromboplastin time (PTT) were measured and recorded by blood test before and after hemoperfusion. The work was reported in line with the STROCSS criteria [19].

Hemoperfusion (HP): To start the process, after placing the filter in the dialysis machine and applying the necessary adjustments, the cartridge and circuit were first washed with normal saline solution and then primed with 4000 international units of unfractionated heparin (UFH) in 1 liter of normal saline. Anticoagulant treatment was performed similar to hemodialysis, which included receiving a bolus dose of 2000 IU of unfractionated heparin, followed by a maintenance dose of 10-12 IU/Kg.hr during the procedure.

The blood flow rate in the device was set between 150-250 cc/min. The first cartridge could usually be used for 4 hours and the next cartridges up to 8 hours. The patients' medication regimen, which included antibiotics and antivirals, was also used after the completion of hemoperfusion.

Statistical analysis: Data were analyzed by SPSS software (Version 23). The normality of quantitative data was evaluated using the one-sample Kolmogorov-Smirnov test, then normal quantitative data were analyzed using the paired t-test, and non-normal data were analyzed using the Wilcoxon test. Also,

sequential qualitative data were analyzed by the Sign test. The significance level was set at 0.05.

Findings

In this study, 49 patients with severe form of COVID-19 disease, who were indicated to receive hemoperfusion based on clinical and laboratory criteria were examined. The average age of the study subjects was 55.5 ± 13.9 years. In terms of gender, there were 22 men (44.9%) and 27 women (55.1%), and in terms of underlying diseases, 11 people had diabetes (22.4%), and 12 people had hypertension (24.4%). The average time of each hemoperfusion session was 4 hours, and the interval between sessions was 1 day on average (minimum 12 hours and maximum 3 days). The average time interval between hemoperfusion and hospitalization was 7 days (between 3 and 24 days). Among the 49 examined patients, 20 (42%) recovered, and 29 (58%) died.

Blood oxygen saturation levels (SpO_2): Examining the data related to the blood oxygen saturation level of the studied patients on the first day, before and after performing hemoperfusion, showed a statistically significant difference (p= .009) so that the average oxygen saturation level before and after performing HP was 86.7±7.2% and 88.5±5.7%, respectively, which indicates an increase and improvement in its level. With further investigation, we noticed the stability of this statistically significant difference on the second and third days of hemoperfusion so that on the second day, this value increased from 85.1±7.7% before HP to 87.4±8.8% after HP (p= .01), and then on the third day, this value increased from 86.9±7.4% before HP to 87.2±8.9% after HP (p= .004) (Table 1).

Excretion factors (urea, creatinine, and albumin): This study results showed that the average urea level increased in the first hemoperfusion session so that the urea level before HP was 73.4±42.4 and after HP was 75.0±45.7, although this increase was not statistically significant (p= .488). Changes in creatinine and albumin levels are also shown in Table 2.

Laboratory symptoms: This study results showed that the average platelet count decreased by 15 units in the first hemoperfusion session so that the platelet count before HP was 255±103 and after HP was 240±106, which was statistically significant (p= .043).

Changes in ESR, WBC, Hb, platelet, and lymphocyte values are also shown in Table 3. In terms of CRP values, the difference between the data in the first session was statistically significant (p= .001) so that in 16 out of 42 cases, the values of this variable after hemoperfusion were lower than the values before HP. In the second hemoperfusion session, the difference between the data was still statistically significant (p= .031) so that in 14 out of 35 cases, a decreasing trend was observed in this variable. Data analysis

Table 1) Changes in blood oxygen saturation values (%)

	HP* (First Session)		HP* (Second Session)		HP* (Third Session)		HP* (Fourth Session)	
	Before	After	Before	After	Before	After	Before	After
Level of SpO_2 (mean±SD**)	86.7 ±7.2	88.5 ±5.7	85.1 ±7.7	87.4 ±8.8	86.9 ±7.4	86.4 ±15.9	84.8 ±6.8	87.4 ±4.7
P value	0.009***		0.01****		0.004***		0.28****	

* HP: hemopefusion; SD: standard deviation; ***: Wilcoxon test; ****: paired t-test

Table 2) Changes in excretion factors (urea, creatinine, and albumin)

	HP* (First Session)		HP* (Second Session)		HP* (Third Session)		HP* (Fourth Session)	
	Before	After	Before	After	Before	After	Before	After
Level of urea (mean±SD**)	73.7 ±42.4	75.0 ± 45.7	76.1 ±44.4	77.1 ±40.6	76.1 ±39.8	76.9 ±35.0	69.2 ±29.0	84.4 ±47.0
P value	0.488***		0.349***		0.482***		0.254****	
Level of creatinine (mean±SD**)	1.39 ±0.65	1.40 ±0.70	1.41 ±0.68	1.36 ±0.64	1.34 ±0.63	1.35 ±0.57	1.28 ±0.26	1.18 ±0.11
P value	0.753***		0.158***		0.421***		0.214***	
Level of Albumin (mean±SD**)	3.30 ±0.33	3.26 ±0.45	3.22 ±0.46	3.02 ±0.37	3.04 ±0.39	2.96 ±0.41	3.05 ±0.21	3.20 ±0.56
P value	0.894****		0.066****		0.372****		0.124****	

* HP: hemoperfusion ; SD: standard deviation; ***: Wilcoxon test; ****: paired t-test

Table 3) Changes in laboratory signs

	HP* (First Session)		HP* (Second Session)		HP* (Third Session)		HP* (Fourth Session)	
	Before	After	Before	After	Before	After	Before	After
Level of ESR† (mean±SD**)	59.40 ±29.9	54.20 ±33.5	53.0 ±34.7	45.80 ±33.7	60.50 ±37.4	38.20 ±32.7	46.2 ±42.1	44.5 ±43.2
P value	0.355****		0.133****		0.344***		0.121***	
Level of WBC†† (mean±SD**)	15.92 ±6.62	17.49 ±7.08	16.49 ±6.15	17.74 ±7.81	17.80 ±7.95	18.00 ±6.68	18.24 ±4.01	17.02 ±6.16
P value	0.110***		0.135***		0.313***		0.562***	
Level of Hb††† (mean±SD**)	14.65 ±8.32	14.81 ±9.34	14.93 ±9.61	15.33 ±13.94	13.72 ±1.87	13.61 ±1.74	12.70 ±1.35	12.90 ±1.71
P value	0.534***		0.758***		0.566****		0.387****	
Level of platelet (mean±SD**)	255 ±103	240 ±106	234 ±105	202 ±95	209 ±78	187 ±75	234 ±106	190 ±75
P value	0.043****		0.001****		0.001****		0.152****	
Level of lymphocyte (mean±SD**)	5.80 ±2.80	6.10 ±3.20	6.0 ±3.30	5.20 ±2.40	5.50 ±2.40	5.20 ±2.10	5.60 ±1.80	4.40 ±1.60
P value	0.174***		0.001***		0.631***		0.109****	

* HP: homoperfusion ; **SD: standard deviation; ***: Wilcoxon test; ****: paired t-test; † ESR: erythrocyte sedimentation rate; ††WBC: white blood cells; †††Hb: hemoglobin

Table 4) Changes in serum electrolytes (calcium, potassium, sodium, phosphorus)

	HP* (First Session)		HP* (Second Session)		HP* (Third Session)		HP* (Fourth Session)	
	Before	After	Before	After	Before	After	Before	After
Level of calcium (mean±SD**)	7.81 ±0.76	7.56 ±0.82	7.60 ±0.79	7.66 ±0.70	7.61 ±0.62	7.71 ±0.67	8.20 ±0.57	8.0 ±0.50
P value	0.638****		0.712****		0.558****		0.217****	
Level of K† (mean±SD**)	4.08 ±0.49	3.99 ±0.52	4.02 ±0.53	4.06 ±0.59	4.08 ±0.57	4.11 ±0.60	3.80 ±0.21	4.18 ±0.30
P value	0.122***		0.555****		0.728****		0.380****	
Level of Na†† (mean±SD**)	136.4 ±4.9	136.9 ±5.1	136.5 ±5.2	137.3 ±4.7	137.3 ±4.8	136.9 ±4.5	139.2 ±5.5	139.0 ±5.3
P value	0.412***		0.160****		0.450***		0.927****	
Level of P††† (mean±SD**)	3.68 ±1.28	3.44 ±0.93	3.49 ±0.94	3.58 ±0.85	3.47 ±0.85	3.89 ±1.85	4.03 ±1.20	3.77 ±1.03
P value	0.562		0.552****		0.886***		0.314****	

* HP: hemoperfusion; **SD: standard deviation; ***: Wilcoxon test; ****: paired t-test; †K: potassium; ††Na: sodium; †††P: phosphorus

Supplementary 1) Changes in CRP levels

	HP* (First Session)	HP* (Second Session)	HP* (Third Session)	HP* (Fourth Session)
Frequency (N)	42	35	27	8
After<Before	16	14	6	3
After=Before	24	17	20	4
After>Before	2	4	1	1
P value	0.001**	0.031**	0.125**	0.321**

* HP: hemoperfusion; **: Sign test

Supplementary 2) Changes in coagulation factors (PT, PTT)

	HP* (First Session)		HP* (Second Session)		HP* (Third Session)		HP* (Fourth Session)	
	Before	After	Before	After	Before	After	Before	After
Level of PT† (mean±SD**)	13.40 ±2.10	14.20 ±4.10	14.90 ±3.0	14.70 ±5.50	15.8 ±5.70	14.70 ±2.90	15.10 ±1.30	15.0 ±2.8
P value	0.021***		0.620***		0.432***		0.254***	
Level of PTT†† (mean±SD**)	31.5 ±8.6	42.0 ±24.7	42.6 ±26.0	39.3 ±26.0	47.2 ±30.3	36.9 ±17.8	40.0 ±14.10	45.2 ±14.1
P value	0.921***		0.452***		0.115***		0.187***	

* HP: hemoperfusion; **SD: standard deviation; ***: Wilcoxon test; ****: paired t-test; †PT: prothrombin time; ††PTT: partial thromboplastin time

in the third session showed no significant difference (p= .125), and a decreasing trend was observed in only 6 out of 27 cases, and in the rest of the cases, no change and stability was observed in CRP values (Appendix 1).

Serum electrolytes (calcium, potassium, sodium, and phosphorus): According to Table 4, the changes in calcium, potassium, and phosphorus levels in the first session before and after hemoperfusion were almost constant and were about 0.5, 0.1, and 0.3 units, respectively. There was no significant relationship between hemoperfusion and any of the above serum electrolytes (p> .005).

Coagulation factors (PT, PTT): Examining the data related to the blood PT values of the studied patients in the first session, before and after hemoperfusion, showed a statistically significant disorder (p= .021), and the mean (± standard deviation) of this variable before and after HP was 13.4±2.1 and 14.2±2.1, respectively. Information about PT and PTT is reported in Appendix 2.

Discussion

By reviewing the literature and studies that have been carried out since the beginning of the COVID-19 epidemic and have continued until now, we come across a wide range of treatment methods used clinically to deal with this disease. The common point of all these methods is that even after a few years of their use, their effectiveness has not been fully proven, and hidden dimensions and aspects of them still remain. One of these treatment methods, which seems to have received less attention than other methods, is the process of hemoperfusion therapy.

This study results showed that the average blood oxygen saturation level of the patients increased and improved after each hemoperfusion session. Several studies have investigated the effect of hemoperfusion on patients' blood SpO_2. Alavi et al. (2023) and Mikaeili et al. (2022) [20, 21] showed that oxygen saturation levels in the hemoperfusion group increased significantly after completing this treatment process, and this change was statistically significant. Statistical tests in the present research also showed the significance of these changes. The reason for the increase and improvement in oxygen saturation levels after hemoperfusion could be related to the decrease in the levels of inflammatory factors, especially IL-6, in the blood of patients. By decreasing the levels of these factors, an inflammatory process occurs in the lung tissue, which leads to apoptosis of vascular cells and an increase in their permeability, the occurrence of acute respiratory distress syndrome (ARDS) is moderated and reduced, and then gas exchanges occur, resulting in improved oxygen saturation levels [22-24].

In the present study, creatinine levels were almost constant before and after the hemoperfusion process, while the studies of Abbasi et al. (2021) [25] and Asgharpour et al. (2020) [26] showed a decrease in creatinine levels after hemoperfusion, and the study of Najafi et al. (2023) reported an increase in creatinine levels [27].

The average urea level also increased by 1 unit after each hemoperfusion session, which is consistent with the results of the study by Najafi et al. (2023) [27], while in the study by Surasit and Srisawat (2022) [28], a decrease in urea level was reported. The molecular weights of creatinine and urea are 113 and 60 daltons, respectively, which are much lower than the filtration range of hemoperfusion filters; thus, theoretically, they are unlikely to be removed and cleaned by hemoperfusion filters. Given the conflicting results, it is suggested that further studies be conducted on the effect of hemoperfusion on creatinine and urea levels.

After hemoperfusion, the patients' blood albumin levels decreased very slightly (the

first session 0.01, the second session 0.17, and the third session 0.08 units); however, these changes were not statistically significant, which is consistent with the results of the study by Peng et al. (2022) [29]. One of the reasons for this issue could be the structure and performance of hemoperfusion filters, the filtration range of the filters used is in the range of materials with a molecular weight of 6 to 60 kilodaltons, and since albumin is a protein with a molecular weight of 68 kilodaltons, it could be concluded that it is not absorbed or very little absorbed by these filters, and its blood level does not undergo significant changes [30].

As a complication of hemoperfusion, blood platelet levels decreased significantly after each session, which is consistent with the results of other studies [20,25,28,29], including the study by Park et al. (2019) [17]. In their study, platelet counts rapidly decreased during the first 30 minutes of hemoperfusion, falling from an average of 242,000 per milliliter of blood to 184,000, and this process continued at a slower rate.

This study results showed that after each hemoperfusion session, plasma CRP levels decreased significantly in the patients studied so that after the first hemoperfusion session, 40% of the patients experienced a decrease in CRP levels. Studies by Siasat et al. (2022) [31] and Abbasi et al. (2021) [25] also showed a significant decrease in CRP levels after the hemoperfusion process. One of the reasons for the decrease in CRP levels after hemoperfusion and the removal of cytokines and inflammatory factors from the body is the decrease in the levels of inflammatory markers [32, 33].

On the other hand, given the filtration range of the filters used in this study and considering the molecular weight of CRP (23 kDa), which is in the middle of this range (between 6 and 60 kDa), it is expected that by performing hemoperfusion, CRP will be separated from the blood, and its blood levels will decrease [30].

Studies on the relationship between hemoperfusion and serum electrolytes are limited. Asgharpour et al. (2020) [26] descriptively reported that serum sodium and potassium levels of patients after three hemoperfusion sessions increased by less than 2%. In general, considering that studies on the relationship between hemoperfusion and serum electrolytes are limited, it is suggested that more studies be conducted in this field [34].

One of the limitations of this study is the existence of financial problems, the high cost of hemoperfusion filters, as well as their limited availability.

Also, due to the lack of access to portable dialysis machines in all medical centers of Golestan province, the lack of trained and skilled personnel, as well as the lack of consent of some patients to buy filters and perform the hemoperfusion procedure, it was not possible to perform it in some medical centers of the province and in some cases. Also, the effect of hemoperfusion on disease outcome and mortality rate was not evaluated.

One of the strengths of this study compared to other studies conducted on patients with COVID-19 is that in this study, the effect of hemoperfusion was investigated on several factors, including blood oxygen saturation levels, excretory factors, inflammatory factors, serum electrolytes, and coagulation factors.

Conclusion

This study results showed that performing hemoperfusion in patients with severe COVID-19 was associated with improvement and increase in blood oxygen saturation values and decrease in CRP values without specific side effects. Since studies conducted on the effect of hemoperfusion on various factors in patients with COVID-19 are limited,

it is recommended that studies with larger sample sizes be conducted, especially by including a control group and investigating potential diagnostic variables.

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Authors' contributions: All authors contributed to the study conception and design. SA and MGG participated in the design of the study. AHS performed data collection. AHS wrote the manuscript. MGG revised the manuscript. MGG contributed to statistical analysis and prepared illustrations. SA edited the manuscript. All authors read and approved the final manuscript.

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